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Utility of ^{18}F-FDG PET and contrast--enhanced CT scan in the assessment of residual liver metastasis from colorectal cancer following adjuvant chemotherapy

Carlo Carnaghi[1], Maria Chiara Tronconi[1], Lorenza Rimassa[1], Luca Tondulli[1], Monica Zuradelli[1], Marcello Rodari[2], Roberto Doci[3], Fabio Luttmann[4], Guido Torzilli[5], Domenico Rubello[6], Adil Al-Nahhas[7], Armando Santoro[1], Arturo Chiti[2]

[1]Department of Oncology, IRCCS Humanitas, Rozzano — Milano, Italy
[2]Department of Nuclear Medicine, IRCCS Humanitas, Rozzano — Milano, Italy
[3]Department of Surgical Oncology, IRCCS Humanitas, Rozzano — Milano, Italy
[4]Department of Radiology, IRCCS Humanitas, Rozzano — Milano, Italy
[5]Department of Liver Surgery, IRCCS Humanitas, Rozzano — Milano, Italy
[6]Service of Nuclear Medicine — PET Unit, S. Maria della Misericordia Hospital, Rovigo, Italy
[7]Department of Nuclear Medicine, Hammersmith Hospital, London, United Kingdom

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Abstract

BACKGROUND: Neoadjuvant chemotherapy has been successfully used in the treatment of patients with colorectal liver metastases. The selection of patients for surgical resection after chemotherapy still poses a significant clinical challenge. ^{18}F-FDG PET is a useful tool in the assessment of liver metastases but the data regarding its sensitivity after chemotherapy is scarce. Our aim was to assess the value of this imaging modality in the selection of patients with colorectal liver metastasis for surgery following adjuvant chemotherapy.

MATERIAL AND METHODS: We reviewed the diagnostic performances of ^{18}F-FDG PET and contrast-enhanced CT scan data from patients with colorectal liver metastases following treatment with chemotherapy. Nineteen patients (12 males, 7 females; median age 61 years; range 41–79) were evaluated. Chemotherapy regimens were: FOLFOX (14 patients), FOLFIRI (3 patients), 5-FU/FA (1 patient) and UFT-irinotecan-oxaliplatin (1 patient). Median time between end of chemotherapy and CT scan was 3.4 weeks, between end of chemotherapy and PET was 5.9 weeks and between end of chemotherapy and surgery was 9.9 weeks. All patients underwent surgery and had histopathological confirmation of liver lesions. Nine patients had segmentectomy, 2 patients had wedge resection, 5 patients had right hepatectomy and 3 patients had explorative laparotomy with liver biopsies.

RESULTS: Data from all 19 patients, comprising 65 liver lesions, were confirmed by histo-pathology. Results on a per-lesion basis showed a sensitivity of 62% for ^{18}F-FDG PET and 70% for CT scan. A complete agreement between ^{18}F-FDG PET or CT scan and histology was documented in 5 and 3 patients, respectively. The sensitivity of ^{18}F-FDG PET was shown to increase for lesions larger than 1 cm (74% *vs.* 18%).

CONCLUSIONS: These results suggest that ^{18}F-FDG PET and CT scan have sub-optimal sensitivity in the evaluation of colorectal liver lesions after neo-adjuvant chemotherapy, especially for lesions < 1 cm. The combined use of the two imaging tech-

Correspondence to: Adil AL-Nahhas
FRCP, Consultant and Chief of Service, Department of Nuclear Medicine, Hammersmith Hospital
Du Cane Road, London W12 0HS, United Kingdom
Tel: +44 208 3834923, fax: +44 208 3831700
e-mail: aal-nahhas@hhnt.org

niques does not significantly increase the sensitivity of lesion detection.

Key words: liver metastases, PET, neoadjuvant chemotherapy, surgery, colorectal cancer

Introduction

The liver is the major site for metastases from colorectal cancer (CRC), and about 40% of patients have metastatic disease confined to the liver at diagnosis or during follow-up. Radical resection of liver metastases offers the best chance of long term survival but this procedure is restricted to a limited number of patients (10%) with few lesions [1], leaving the majority of patients (90%) unsuitable for surgery. For these patients systemic chemotherapy is the standard treatment. Systemic fluoropirimidine based regimens achieve a response rate between 15% and 30%, with a median survival of approximately 12 months. The introduction in clinical practice of new agents such as irinotecan and oxaliplatin, administered in combination with 5-fluorouracil (5-FU) led to a dramatic increase of response rate (40–50%) and to a significant prolongation of survival (approximately 20 months). Moreover, these drugs have been shown to downstage liver disease in patients with non resectable metastases, leading to a better long-term survival with surgical resection of residual liver disease. It is therefore critical to identify an accurate diagnostic imaging me-thod to restage patients with liver disease after chemotherapy. The standard diagnostic procedure employed to assess the extension of liver disease before and after chemotherapy is contrast-enhanced CT scan but this modality is flawed by the lack of sensitivity in distinguishing between residual disease and scar or necrotic tissue [2]. Positron emission tomography (PET), using fluorine-18-deoxyglucose (^{18}F-FDG) has been assessed as one of the more effective diagnostic modalities to study colorectal cancer, thanks to its ability to detect active, glucose-avid, tumor sites. The introduction of ^{18}F-FDG PET in the diagnostic work-up of patients with resectable CRC liver metastases had a significant impact on patients' management [3] but clinical data on the role of ^{18}F-FDG PET in patients treated with neo-adjuvant chemotherapy with apparent resectable hepatic metastases is very limited [4]. Furthermore, it has been suggested that modification of some biologic characteristics induced by chemotherapy, such as reduction of Ki-67 or decrease in hexokinase activity, could lower ^{18}F-FDG-PET sensitivity [4, 5].

The aim of our study was to retrospectively evaluate the diagnostic sensitivity of ^{18}F-FDG PET and CT scan in patients with liver metastases from CRC treated with pre-surgical chemotherapy.

Material and methods

In this retrospective analysis we reviewed data from 19 patients with unresectable colorectal liver metastases treated with neo-adjuvant/pre-surgical chemotherapy at IRCCS Humanitas, between October 2002 and February 2006. The patients' characteristics are summarized in Table 1. There were 12 males and 7 females, with a median age of 61 years (range 41–79). Twelve patients presented with synchronous liver metastases and seven with metachronous metastases. All patients had radical surgery of the primary tumor before chemotherapy. Chemotherapy regimens were: FOLFOX-4 (14 patients), FOLFIRI (3 patients), 5-FU//FA (1 patient) and UFT-irinotecan-oxaliplatin (1 patient). Following completion of chemotherapy, the patients were evaluated with ^{18}F-FDG PET and CT scan before hepatic resection. Whole-body PET scan in 3D mode was performed using a Siemens Ecat Accel LSO full-ring scanner, 60 minutes after the injection of 310–450 MBq ^{18}F-FDG. Contrast-enhanced, 3-phase liver CT scan was performed using a Philips aura single slice system. Imaging results were considered independently by 2 experienced, radiologists/nuclear medicine specialists. The mean time between the end of chemotherapy and CT scan was 3.4 weeks; between the end of chemotherapy and ^{18}F-FDG PET was 5.9 weeks and between CT scan and ^{18}F-FDG PET was 3 weeks. All CT and ^{18}F-FDG PET scans were performed within 2 months from laparotomy. After imaging, all patients underwent laparotomy for resection of residual liver metastases and exploration of liver parenchyma in order to find unidentified metastases. Surgery included 6 major hepatectomies, 7 segmentectomies, 4 metastasectomies, 4 biopsies, and 2 radiofrequency ablation. All patients had histological confirmation of the liver lesions and in most of the patients a significant downstage of liver disease was documented. These pathologic findings were correlated with CT scan and ^{18}F-FDG PET results. All imaging results were classified as true positive, false positive true negative or false negative. Sensitivity and po-sitive predictive values were calculat-

Table 1. Patients characteristics

	Number of patients (%)
Evaluable patients	19 (100%)
Sex	
Male	12 (63%)
Female	7 (37%)
Median age (range)	61 yrs (41–79)
Primary tumor site	
Colon	14 (74%)
Rectum	5 (26%)
Metastases	
Synchronous	12 (63%)
Metachronous	7 (37%)
Neo-adjuvant chemotherapy	
FOLFOX-4	14 (74%)
FOLFIRI	3 (16%)
5-FU/FA	1 (5%)
UFT-irinotecan-oxalipatin	1 (5%)
Median duration of chemotherapy (range)	15.9 weeks (2–47)
Surgery	
Right hepatectomy	5 (26%)
Metastasectomy	2 (11%)
Segmentectomy	9 (47%)
Other (biopsy, RF)	3 (16%)
Blood glucose level at ^{18}F-FDG PET injection	
> 120 mg/dl	1 (5%)
100–120 mg/dl	2 (11%)
< 100 mg/dl	16 (84%)
Median interval between procedures (range)	
End of Chemo → CT	3.4 weeks (1–33)
End of Chemo → ^{18}F-FDG PET	5.9 weeks (2–36)
End of Chemo → Surgery	9.9 weeks (5–42)
CT → ^{18}F-FDG PET	3 weeks (0–14)
CT → Surgery	6.6 weeks (1–14)
^{18}F-FDG PET → Surgery	3.6 weeks (0–17)

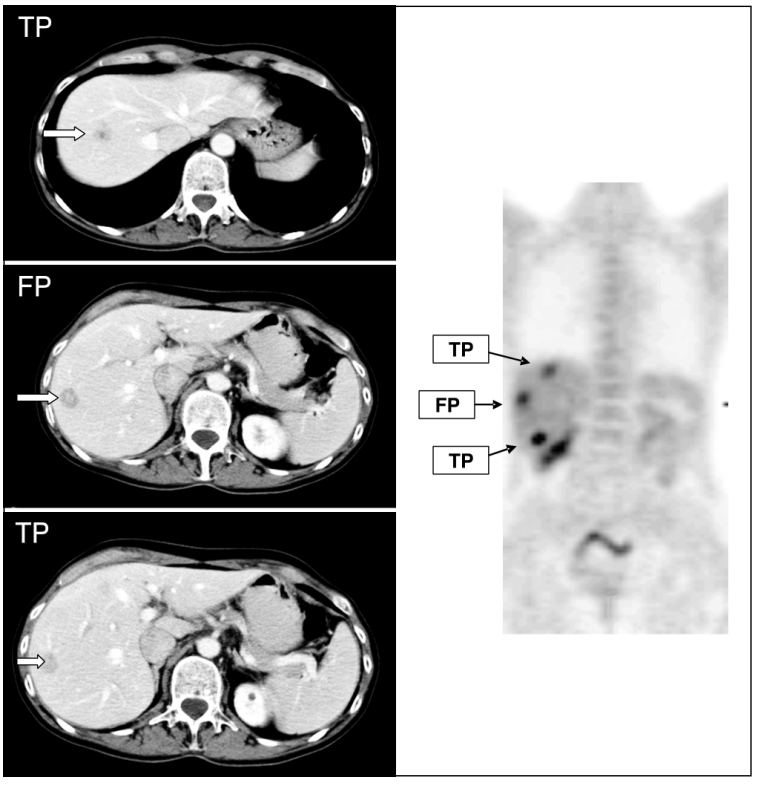

Figure 1. Example of a patient with 3 liver lesions, of which 1 was false positive and 2 were true positive The false positive lesion was attributed to inflammatory lesions induced by cellular infiltration after chemotherapy. Note there is no significant difference in the morphology and in the metabolic aspect of the 3 different lesions. CT scan is illustrated on the left (3 panels) and PET (coronal view) is on the right. TP — true positive; FP — false positive.

ed. Specificity could not be calculated because the presence of liver disease was a selection criterion.

Results

All patients underwent surgical liver resection with curative aim, having demonstrated the absence of extra-hepatic disease at preoperative ^{18}F-FDG PET and CT scan. On the 19 evaluable patients, 65 liver metastases were detected by histophatologic examination of surgical specimens. At laparotomy extrahepatic disease was detected in 4 patients (21%): coeliac lymph node involvement in 3 cases and peritoneal carcinomatosis in one.

Whole-body ^{18}F-FDG PET detected 47 liver lesions. Forty of these were confirmed by histopathology, resulting in a sensitivity for ^{18}F-FDG PET of 62%. Sensitivity was strongly associated with the diameter of the metastases; the sensitivity for lesions smaller than 1 cm was only 18% while that of lesions larger than 1 cm was 74%. Seven cases of unexplained ^{18}F-FDG PET false-positive liver uptake were documented (Figure 1).

CT scan detected 59 liver metastases. Forty-five of these were confirmed by histopathology, resulting in a CT scan sensitivity of 70%. There were 14 false positives, most of which were scar or necrotic tissue. The sensitivity of CT scan for lesions < 1 cm (41%) was higher than that of ^{18}F-FDG PET (18%).

^{18}F-FDG PET corrected a false-positive CT scan result in 2 patients, while CT scan identified 6 liver metastases not detectable at ^{18}F-FDG PET. The combined use of the two techniques achieved a small improvement in terms of sensitivity (75%).

Table 2. Comparison of ^{18}F-FDG PET and CT scan results according to histology (65 lesions). Per lesion analysis

Modality	TP (%)	FN (%)	FP (%)	Sensitivity (%)	PPV (%)
CT scan	45	20	14	69	76
^{18}F-FDG PET	40	25	7	62	85
CT scan + + ^{18}FF-FDG PET				74	78

TP — true positive; FN — false negative; FP — false positive; PPV — positive predictive value; CT — computed tomography

In a "per patient" analysis CT scan achieved a complete agreement with histopathological data in 3 patients (5%) and ^{18}F-FDG PET in 5 patients (8%).

Positive predictive value (PPV) was calculated as 76% for CT scan, 85% for ^{18}F-FDG PET and 78% for the combination of the two modalities.

These results are summarized in Table 2.

Discussion

CT scan is currently regarded as one of the best method for evaluating resectability of CRC liver metastases. Many recent studies underlined the added value of ^{18}F-FDG PET in staging patients with liver CRC metastases identifying patients who will benefit from resection and excluding those who will not [6, 7]. ^{18}F-FDG PET has been reported to have a higher accuracy for detection of hepatic metastases (90%) compared to CT scan (70%), indicating

a possible role in the determination of lesion number and lobar distribution, but these data have been achieved in patients who have not been treated with chemotherapy [8–10].

In order to evaluate the performances of ^{18}F-FDG PET and CT imaging at the end of neo-adjuvant chemotherapy, we reviewed the results achieved in 19 patients who underwent liver resection for CRC liver metastases. In terms of sensitivity our results are disappointing for ^{18}F-FDG PET (62%), for CT scan (69%) and for the combined use of the two modalities (75%). In our study ^{18}F-FDG PET sensitivity was particularly low for lesions smaller than 1 cm (18%). This reduction of sensitivity in treated patients could be the result of altered ^{18}F-FDG uptake, most likely related to chemotherapy induced decrease of tumor cells hexokinase activity [11]. A low sensitivity of ^{18}F-FDG PET for small liver metastases was also documented in other studies in untreated and treated patients [4, 10]. In these small trials a strong correlation between lesion size and capability of detection by ^{18}F-FDG PET has been shown. In our study we selected patients without evidence of extrahepatic disease at preoperative staging by ^{18}F-FDG PET and CT scan, but in four patients laparotomy and subsequent histological examination identified extrahepatic disease. It is worth noting that all extrahepatic disease sites (celiac nodal involvement and peritoneal carcinomatosis) were very close to the liver. These lesions were undetectable by CT scan and wrongly localized as hepatic disease by ^{18}F-FDG PET.

The high rate of false positives affected the results in term of PPV for ^{18}F-FDG PET (85%) and CT scan (76%). These results are disappointing if compared with the studies conducted on chemonaive patients [4, 10, 12–14]. The false positive lesions at ^{18}F-FDG PET were unexplained in 4 cases, related to extrahepatic nodal involvement close to the liver in 2 cases, and to the presence of granulomatous tissue in one. It is also possible that false positive lesions were related to post-therapy inflammatory changes. On the contrary, the 14 false positive lesions observed by CT scan were all attributable to scar or necrotic tissue near to previous metastatic liver lesions. Finally, the results are particularly disappointing in a "per patient" analysis in which a complete agreement between ^{18}F-FDG PET and CT scan, and histological data have been achieved in a limited number of patients (5 patients for ^{18}F-FDG PET and 3 patients for CT scan).

Conclusions

Our results suggest that ^{18}F-FDG PET and CT scan have reduced sensitivity for evaluation of CRC liver lesions after neo-adjuvant chemotherapy, in particular for lesions < 1 cm. On these bases ^{18}F-FDG PET should not be recommended as a routine staging procedure after neo-adjuvant chemotherapy, but should be performed before chemotherapy in order to identify extra-hepatic disease and avoid unnecessary surgical procedures. The combined use of ^{18}F-FDG PET and CT scan does not offer an improvement in sensitivity. Larger prospective trials are warranted to define more precisely the role and utility of ^{18}F-FDG PET in this clinical setting.

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